



NTP
National Toxicology Program

Drug Matrix DB: a Large Toxicogenomic Reference Resource



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Division, National Toxicology Program

National Institute of Environmental Health Sciences





Outline

- Part 1: General Introduction to DrugMatrix and ToxFX
- Part 2: Overview of the DrugMatrix Database



DrugMatrix®

Scott S. Auerbach, PhD - Coordinator; auerbachs@niehs.nih.gov
Dan Svoboda, PhD - DB Manager

Register to Use DrugMatrix →

Recover/Reset password →

Launch DrugMatrix →

Upload Experiments into DrugMatrix →

History, Contributors, Publications →

Download DrugMatrix Array Data →

Section 508 Accommodation →

Go to ToxFX →

Information for getting started:

- Software requirements: Internet Explorer
- Supported platforms and data formats for upload:

Supported microarrays

Codelink Rat Uniset 1

Affymetrix Rat Genome 230 2.0

Affymetrix Rat Genome U34A

Affymetrix Rat Expression 230A

Affymetrix Rat Focus Array Plate

Required data format

Tab-delimited text files

PLIER CHP files

PLIER CHP files

PLIER CHP files

PLIER CHP files

Note: PLIER normalized CHP files can be generated from Affymetrix CEL files using Expression Console™

- A DrugMatrix manual and tutorial are located in the "Help" section (upper right) on the homepage following log in. New users are encouraged to review the tutorial before using DrugMatrix to conduct analysis of their own data. Please note, such data would need to be uploaded to DrugMatrix and are not accessible to other users.
- In order to view some of the chemical structures in DrugMatrix the CHIME web plug-in is required.

DrugMatrix and ToxFX: History

- DrugMatrix
 - Comprehensive Rat Toxicogenomics Database and Analysis Tool
 - <https://ntp.niehs.nih.gov/drugmatrix/index.html>
- ToxFX
 - Automated Toxicogenomics Analysis Tool that uses DrugMatrix data and signatures to evaluate user data
 - <https://ntp.niehs.nih.gov/toxfx/>
- Originally owned by Iconix Pharmaceuticals and Entelos, Inc.
- Acquired by NTP in late 2010
 - Goal
 - Facilitate the integration of toxicogenomics into hazard characterization
 - Make the computational and data resources **freely available to the public**



DrugMatrix: Applications

- Upload your own data for analysis or mine the DrugMatrix data
- Find similar expression profiles
- Determine significantly up and down regulated genes
- Perform gene ontology analysis of perturbed genes
- Visualize expression profiles on pathways
- Score expression profiles for >50 phenotypes with Drug Signatures
- Construct expression patterns for putative biomarker sets
- Test the performance of biomarker sets for detecting phenotypes
- Perform hierarchical clustering
- Find consistently changed genes
- Identify enriched literature annotations in groups of expression profiles
- Mine the literature



DrugMatrix: Upload data

DrugMatrix Online Study Builder 2.0.0

Studies Experiments Arrays

Study Name: New Study Study Title: Test Compou...
Compound: 1,2-dichloro... Tissue: LIVER

Upload Study

Study Panel Experiments QC

Save Study

| | Values |
|-----------------------------|--------------------|
| Study Fields | |
| Study Title | Test Compound |
| Institution | NIEHS |
| Study Designation | Test Study |
| Target Preparation Protocol | RNA |
| Compound | 1,2-dichloroethene |
| Study Tissue | LIVER |
| Array Platform | RatToxFX |
| Dose mg/kg (not enterable) | |
| Days Dosing (not enterable) | |
| Dosing Frequency | Daily |
| Vehicle | Water |
| Route of Administration | Intraperitoneal |
| Strain | Fisher |
| Age | 120 days |
| Sex | Male |
| Weight | 300g |
| Additional Data | |



DrugMatrix: Upload data

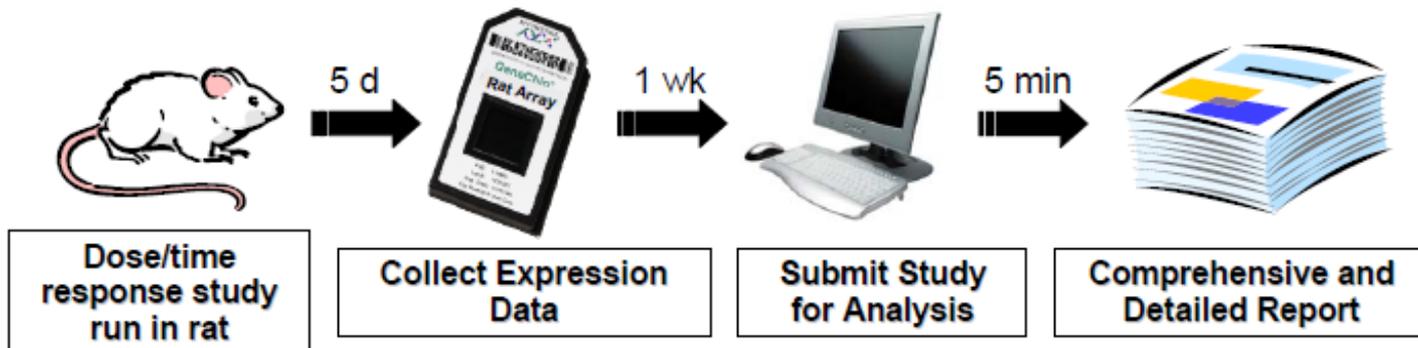
| | Values |
|-----------------------------|--------------------|
| Study Fields | |
| Study Title | Test Compound |
| Institution | NIEHS |
| Study Designation | Test Study |
| Target Preparation Protocol | RNA |
| Compound | 1,2-dichloroethene |
| Study Tissue | LIVER ▼ |
| Array Platform | RatToxFX ▼ |
| Dose mg/kg (not enterable) | |
| Days Dosing (not enterable) | |
| Dosing Frequency | Daily ▼ |
| Vehicle | Water ▼ |
| Route of Administration | Intraperitoneal ▼ |
| Strain | Fisher ▼ |
| Age | 120 days |
| Sex | Male ▼ |
| Weight | 300g |
| Additional Data | |

- Brain
- Heart
- Hepatocyte
- Intestine
- Kidney
- Liver
- Spleen
- Thigh Muscle
- HT Rat-Focus
- Rat 230 2.0
- Rat Exp Array 230A
- Rat Genome U34A
- RatToxFX
- Daily
- Weekly
- Multiple Daily
- Corn Oil
- Saline
- Water
- Intraperitoneal
- Intravenous
- Oral Gavage
- Fisher
- Sprague Dawley
- Male
- Female



ToxFX

- Rapid, automated toxicogenomic analysis tool
- Generates a detail toxicogenomics report within 5 minutes
 - Ranking of the relative toxicological liabilities of their compound
 - Quality control analysis which ensures the highest quality data
 - Choice of 3 comparator compounds, available from the DrugMatrix[®] database
 - Tailored report, written to append to existing toxicology study reports
 - Increased productivity – saving time on analysis and report-writing





DrugMatrix vs. ToxFX

- ToxFX and DrugMatrix provide toxicogenomics analyses but were developed for different end users

| Feature | ToxFX | DrugMatrix |
|------------------|------------------|---------------------|
| Customizable | No | Yes |
| Depth | Quick comparison | Comprehensive |
| Expertise needed | No | Yes |
| Resources needed | Data only | Data and Scientists |
| Time | <1 day | Open-ended |
| Drug Signatures | Yes | Yes |
| Pathway Analysis | Yes | Yes |
| DEGs | Yes | Yes |



Drug/Toxicity Signatures (1)

| Examples of Drug Signatures Classes | Toxicological Outcomes |
|--|--|
| Toxicity Endpoint | DNA Alkylator, Heavy Metal Toxicant, Renal DNA Intercalator (Anthracycline-like) |
| Organ Pathology | Hepatic Necrosis, Bile Duct Hyperplasia, Renal Tubular Necrosis, Nephromegaly, Cardiac Myocyte Degeneration, Heart Weight Increase |
| Genetic Endpoint | DNA Damage |
| Mechanistic Class | PXR Activation, Peroxisome Proliferator |



Drug/Toxicity Signatures (2)

- Signatures available on liver, heart, kidney, and thigh muscle.
- DrugMatrix has hundreds of signatures on these four organs & primary hepatocytes.
- ToxFX encompasses all DrugMatrix Affymetrix data for liver, heart, kidney, and primary hepatocytes, but not muscle.
- ToxFX has 27 liver signatures and 55 total signatures covering liver, heart, or kidney and 8 primary hepatocyte signatures.
- 8 primary hepatocyte signatures



DrugMatrix Data

Download DrugMatrix Array Data 

- <ftp://anonftp.niehs.nih.gov/drugmatrix>
- Unprocessed microarray data
 - Bulk download
 - Individual Expression Studies
- Microarray data normalized by organ
 - Affymetrix – 5 normalization algorithms
 - Codelink – Quantile normalized
- Individual animal toxicology data
- Detailed array parameter files



DrugMatrix: FTP Download

FTP root at anonftp.niehs.nih.gov

| | | | |
|--------------------|-------------|--|--|
| 12/17/2012 08:39PM | Directory | drugmatrix | |
| 10/25/2012 12:00AM | Directory | ntp | |
| 06/21/2012 12:00AM | Directory | ntp-cebs | |
| 03/08/2011 12:00AM | Directory | roc | |
| | | | |
| 02/24/2012 12:00AM | Directory | Affymetrix data | |
| 02/24/2012 12:00AM | Directory | Codelink data | |
| 05/17/2012 12:00AM | Directory | Compound Literature Annotations | |
| 05/16/2012 12:00AM | Directory | Differential Gene Expression Data | |
| 05/18/2012 12:00AM | Directory | DrugMatrix Manual and Tutorials | |
| 05/17/2012 12:00AM | Directory | In Vitro Assay Data | |
| 04/05/2012 12:00AM | Directory | Individual Animal Toxicology Data | |
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| 10/11/2011 12:00AM | 74,847 | Affymetrix treated to control microarray mapping.zip | |
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| 12/09/2011 12:00AM | Directory | Individual experiments | |
| 12/09/2011 12:00AM | Directory | Normalized data by organ | |
| 02/24/2012 12:00AM | Directory | old data labels spreadsheets | |
| | | | |
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| 12/14/2011 12:00AM | Directory | HEPATOCYTES | |
| 12/14/2011 12:00AM | Directory | KIDNEY | |
| 12/14/2011 12:00AM | Directory | LIVER | |
| 12/14/2011 12:00AM | Directory | THIGH-MUSCLE | |
| | | | |
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| 12/14/2011 12:00AM | 83,240,705 | 1-NAPHTHYL ISOTHIOCYANATE.zip | |
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| 12/14/2011 12:00AM | 20,998,022 | ALPHA-NAPHTHOFLAVONE.zip | |
| 12/14/2011 12:00AM | 85,431,063 | ALTRETAMINE.zip | |
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<ftp://anonftp.niehs.nih.gov/drugmatrix/>



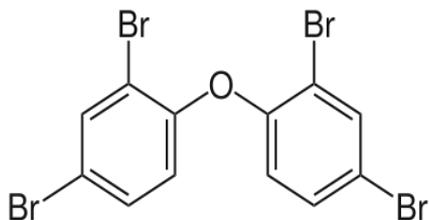
Example Application of DrugMatrix

DE-71

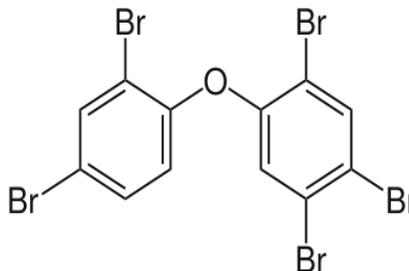
(Study Scientist: Dr. June Dunnick)



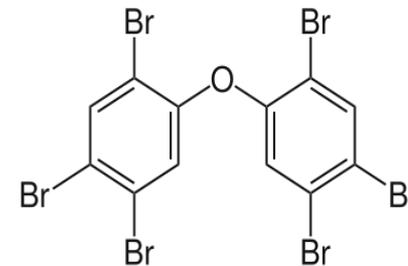
DE71: A mixture of polybrominated diphenyl ethers



BDE 47



BDE 99



BDE 153

- PBDEs are flame retardant components that bioaccumulate; persistent organic pollutants
- Widespread human exposure
- Hepatic enzyme inducing agents and endocrine disruptors



Gene Expression Study design

- Dose level: 0 or 50 mg/kg/day
- Route: Oral Gavage (methylcellulose)
- Model: Male Wistar Han rats
- Exposure period: gestational day (GD) 6 to postnatal day (PND) 21
- Euthanized: PND 22
- Tissue evaluated: Liver
- Array: Affymetrix Rat Genome 230 2.0
- Question: What are the potential toxicological effects of DE71 that can be identified by toxicogenomics?

DrugMatrix Analysis of DE71- Top DEGs

- Cyp1a1, Cyp2b, Cyp2c

- Fgf21, Cyp17a1, Abcg8

Induced

Repressed

| SIMILAR | INDUCED | REPPRESSED | DENDROGRAM | CLIN. PATH. | MOTIF | SPLP | TRANK | HISTOPATHOLOGY |
|--|---------------------|------------|------------|-------------|-------|------|-------|----------------|
| <input checked="" type="checkbox"/> MENU TRANSCRIPTIONAL RESPONSES (INDUCED) | | | | | | | | |
| GENE | CONFIDENCE INTERVAL | P VALUE | | | | | | |
| <input checked="" type="checkbox"/> urinary protein 2 (1370396_x_at,rc_AA945585_at) | | 2.68E-10 | | | | | | |
| <input checked="" type="checkbox"/> urinary protein 2 (1370349_a_at) | | 1.41E-10 | | | | | | |
| <input checked="" type="checkbox"/> estrogen sulfotransferase (1368733_at,M86758_at,NM_012883_PROBE1) | | 9.59E-8 | | | | | | |
| <input checked="" type="checkbox"/> cytochrome P450, family 2, subfamily A, polypeptide 3a (1369136_at) | | 1.07E-10 | | | | | | |
| <input checked="" type="checkbox"/> transmembrane protein 27 (1387013_at,NM_020976_PROBE1) | | 3.49E-9 | | | | | | |
| <input checked="" type="checkbox"/> CEA-related cell adhesion molecule 10 (Non-specific probe) (1370371_a_at) | | 1.78E-11 | | | | | | |
| <input checked="" type="checkbox"/> urinary protein 2 (1389270_x_at) | | 1.87E-5 | | | | | | |
| <input checked="" type="checkbox"/> cytochrome P450, family 2, subfamily c, polypeptide 29 (DBSS_moderate) (139615...) | | 0.00E0 | | | | | | |
| <input checked="" type="checkbox"/> Kruppel-like factor 2 (lung) (DBSS) (1386040_at) | | 1.11E-12 | | | | | | |
| <input checked="" type="checkbox"/> CLIP associating protein 2 (1396604_at) | | 1.50E-7 | | | | | | |
| <input checked="" type="checkbox"/> Iroquois related homeobox 2 (Drosophila) (1391457_a_at) | | 1.30E-9 | | | | | | |
| <input checked="" type="checkbox"/> cytochrome P450, family 1, subfamily a, polypeptide 1 (1370269_at) | | 1.63E-6 | | | | | | |
| <input checked="" type="checkbox"/> cytochrome P450 2c13 (1370495_s_at,M82855cde_s_at) | | 7.54E-6 | | | | | | |
| <input checked="" type="checkbox"/> RT1 class I, CE10 (1388202_at) | | 1.14E-4 | | | | | | |
| <input checked="" type="checkbox"/> Cytochrome P450 2C24 (CYP11C24) (P450-PROS2) (DBSS) (1370241_at,M18335_f...) | | 1.14E-9 | | | | | | |
| <input checked="" type="checkbox"/> ESTs (1397343_at) | | 8.82E-8 | | | | | | |
| <input checked="" type="checkbox"/> Transcribed locus (1380543_at) | | 7.32E-10 | | | | | | |
| <input checked="" type="checkbox"/> cytochrome P450, family 2, subfamily b, polypeptide 13 (1387993_at) | | 2.69E-8 | | | | | | |
| <input checked="" type="checkbox"/> leptin (1387748_at) | | 9.76E-8 | | | | | | |
| <input checked="" type="checkbox"/> MGC14161 protein (DBSS) (1396720_at) | | 1.50E-7 | | | | | | |

| SIMILAR | INDUCED | REPPRESSED | DENDROGRAM | CLIN. PATH. | MOTIF | SPLP | TRANK | HISTOPATHOLOGY |
|--|---------------------|------------|------------|-------------|-------|------|-------|----------------|
| <input checked="" type="checkbox"/> MENU TRANSCRIPTIONAL RESPONSES (REPPRESSED) | | | | | | | | |
| GENE | CONFIDENCE INTERVAL | P VALUE | | | | | | |
| <input checked="" type="checkbox"/> hypothetical protein FLJ32871 (DBSS) (1394309_at) | | 6.62E-11 | | | | | | |
| <input checked="" type="checkbox"/> ABO blood group (transferase A, alpha 1-3-N-acetylglactosaminyltransfer...) | | 3.68E-5 | | | | | | |
| <input checked="" type="checkbox"/> protein phosphatase 2 (formerly 2A), regulatory subunit B (PR 52), beta is... | | 3.61E-6 | | | | | | |
| <input checked="" type="checkbox"/> CDNA clone IMAGE:7460165 (1371298_at) | | 5.89E-11 | | | | | | |
| <input checked="" type="checkbox"/> olfactory receptor 1696 (1370741_at) | | 8.72E-5 | | | | | | |
| <input checked="" type="checkbox"/> fibroblast growth factor 21 (1387643_at) | | 3.48E-6 | | | | | | |
| <input checked="" type="checkbox"/> N-terminal acetyltransferase 1 (DBSS) (1381204_at) | | 6.13E-5 | | | | | | |
| <input checked="" type="checkbox"/> ESTs (1392613_at) | | 9.46E-6 | | | | | | |
| <input checked="" type="checkbox"/> ESTs (1379156_at) | | 2.07E-5 | | | | | | |
| <input checked="" type="checkbox"/> nuclear factor, erythroid derived 2 (1375040_at,BF397726_PROBE1) | | 2.09E-6 | | | | | | |
| <input checked="" type="checkbox"/> low-density lipoprotein receptor-related protein 10 (Non-specific probe) (1... | | 1.45E-6 | | | | | | |
| <input checked="" type="checkbox"/> F-box protein FBL2 (DBSS) (1381961_at) | | 1.06E-2 | | | | | | |
| <input checked="" type="checkbox"/> Transcribed locus (1381317_at) | | 5.61E-3 | | | | | | |
| <input checked="" type="checkbox"/> cytochrome P450, family 17, subfamily a, polypeptide 1 (1387123_at,M21... | | 1.77E-7 | | | | | | |
| <input checked="" type="checkbox"/> sorting nexin associated golgi protein 1 (DBSS) (1390064_at) | | 2.18E-3 | | | | | | |
| <input checked="" type="checkbox"/> Transcribed locus (1380306_at) | | 3.14E-5 | | | | | | |
| <input checked="" type="checkbox"/> alpha-2-macroglobulin (1367794_at,J02635_PROBE1) | | 4.14E-6 | | | | | | |
| <input checked="" type="checkbox"/> ATP-binding cassette, sub-family G (WHITE), member 8 (1369440_at) | | 3.65E-5 | | | | | | |
| <input checked="" type="checkbox"/> hypothetical protein MGC35130 (DBSS) (1386132_at) | | 2.10E-4 | | | | | | |
| <input checked="" type="checkbox"/> ESTs (1374610_at,AI599365_PROBE1) | | 2.59E-4 | | | | | | |

DrugMatrix Analysis of DE71- Signature Scoring

DE71_21.0D_50.0MG/KG_LIVER

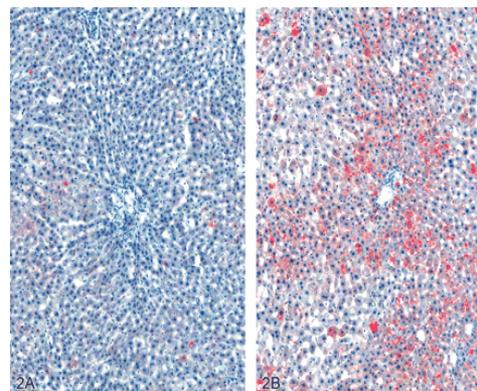
TRANSOR. RESP.

SIMILAR | INDUCED | REPRESSED | DENDROGRAM | CLIN. PATH. | MOTIF | SPLP | TRANK | HISTOPATHOLOGY

> MENU DRUG CLASSIFIER

| SIGNATURE NAME | SP SCORE | POSTERIOR | LOGIT | DERIVATION |
|--|----------|----------------|--------------|------------|
| <input checked="" type="checkbox"/> Hepatic hypertrophy, centrilobular LIVER RG230-2 ASPLP ToxFX.1.2.4 | 2.668 | 0.999835654... | 6.9067547... | RG230-2 |
| <input checked="" type="checkbox"/> Hepatic lipid accumulation, centrilobular LIVER RG230-2 SPLP ToxFX.1.2.4 | 0.93 | 0.902890876... | 2.2297663... | RG230-2 |
| <input checked="" type="checkbox"/> Hepatic lipid accumulation, macrovesicular LIVER RG230-2 ASPLP ToxFX.1.2.4 | 0.482 | 0.873777575... | 1.9347802... | RG230-2 |
| <input checked="" type="checkbox"/> Hepatic lipid accumulation, periportal LIVER RG230-2 SPLP ToxFX.1.2.4 | 0.192 | 0.776136029... | 1.2432892... | RG230-2 |
| <input checked="" type="checkbox"/> Hepatomegaly LIVER RG230-2 ASPLP ToxFX.1.2.4 | 0.292 | 0.775934833... | 1.2421316... | RG230-2 |

Rat Liver - Oil Red O



Vehicle

DE71

Dunnick, *et al*, Tox. Path., 2012



DrugMatrix Analysis of DE71- Chemical Enrichment Analysis

- Chemical ontology enrichment analysis of the top 25 most similar expression studies (Hypergeometric Analysis)

| | A | B | C |
|----|--------------------|--|----------|
| 1 | CATEGORY | TERM | PVALUE |
| 2 | MECH_LEVEL_3 | aromatase | 4.17E-06 |
| 3 | MECH_LEVEL_2 | Inhibit estrogen biosynthesis | 4.44E-06 |
| 4 | SOLVENT | CMC .5 % | 8.35E-06 |
| 5 | ADVERSE_EFFECT | BBM_2_Bone Marrow Toxicity | 1.07E-06 |
| 6 | ADVERSE_EFFECT | NEU_1_Ataxia | 3.35E-06 |
| 7 | ADVERSE_EFFECT | END_2_Acute Intermittent Porphyria | 1.07E-06 |
| 8 | ADVERSE_EFFECT | KID_3_Acute Tubular Necrosis | 1.07E-06 |
| 9 | STRUCTURE_ACTIVITY | NSAID, COX-3, antipyrine like | 1.07E-06 |
| 10 | STRUCTURE_ACTIVITY | Estrogen antagonist, aromatase inhibitor | 6.99E-07 |

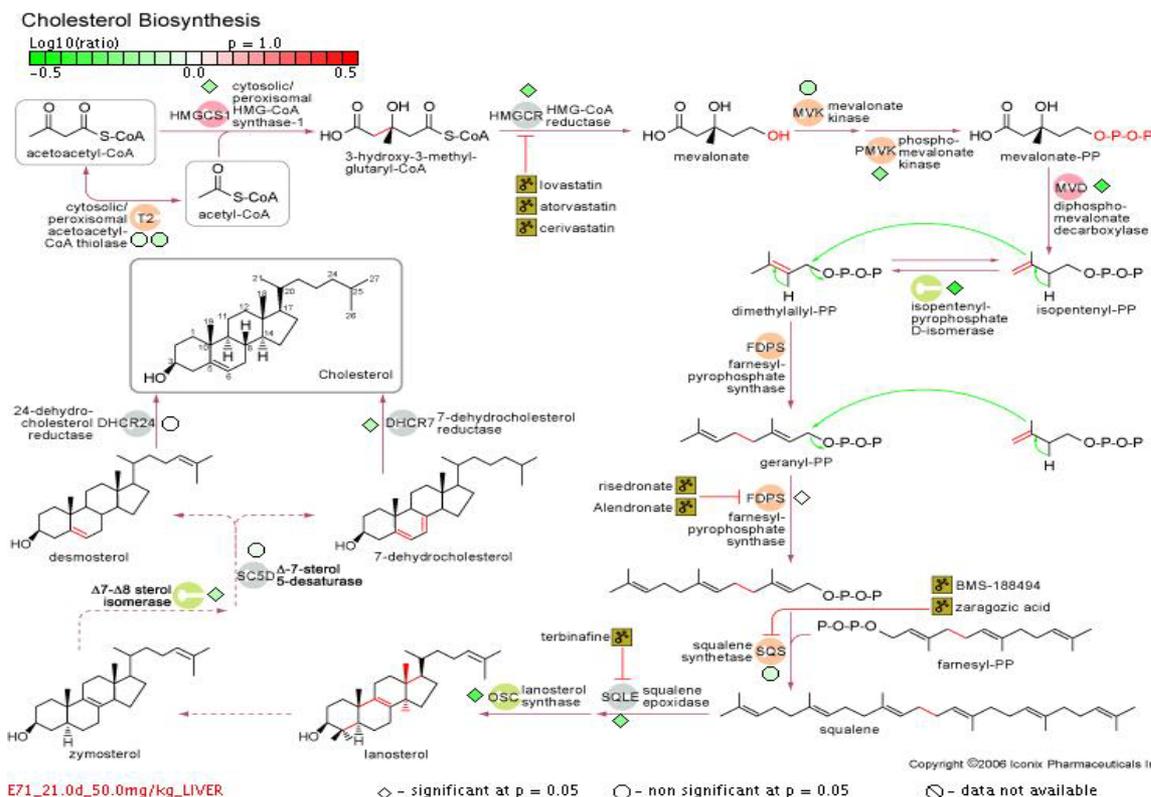
* DE71 has been shown to alter aromatase activity in number of studies



DrugMatrix Analysis of DE71- Pathway Analysis

| Pathway | % Gene Changed in Pathway |
|--|---------------------------|
| Cholesterol Biosynthesis | 75 |
| Xenobiotic Metabolism | 51.724136 |
| Bile Acid Synthesis | 50 |
| Bile Acid & Cholesterol Metabolism | 45.833336 |
| Oxidative Stress Response Mediated by Nrf2 | 44.897957 |

*Multiple subchronic studies have observed increases in serum cholesterol following DE71 exposure

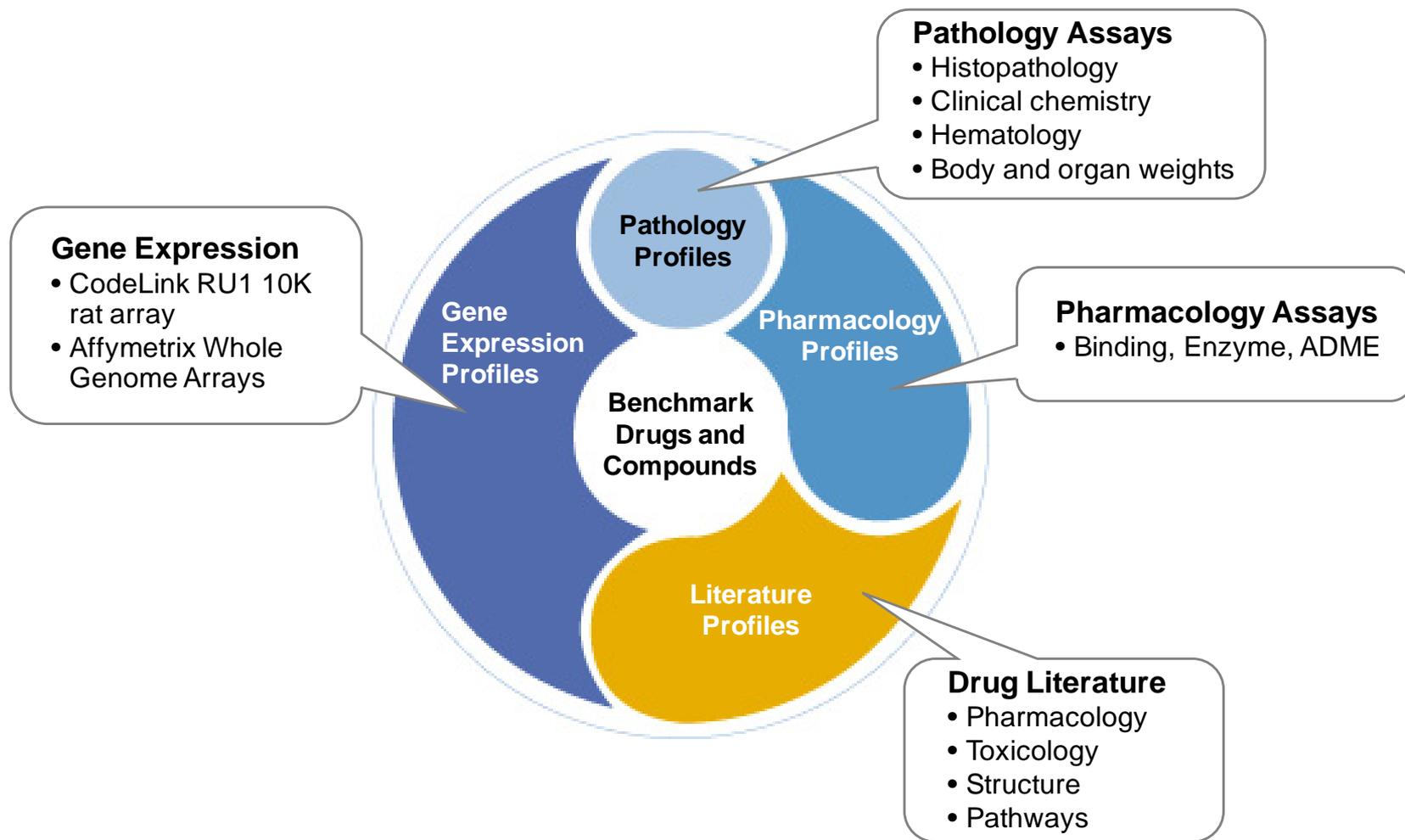




Part 2: DrugMatrix Database Overview



DrugMatrix Database Content

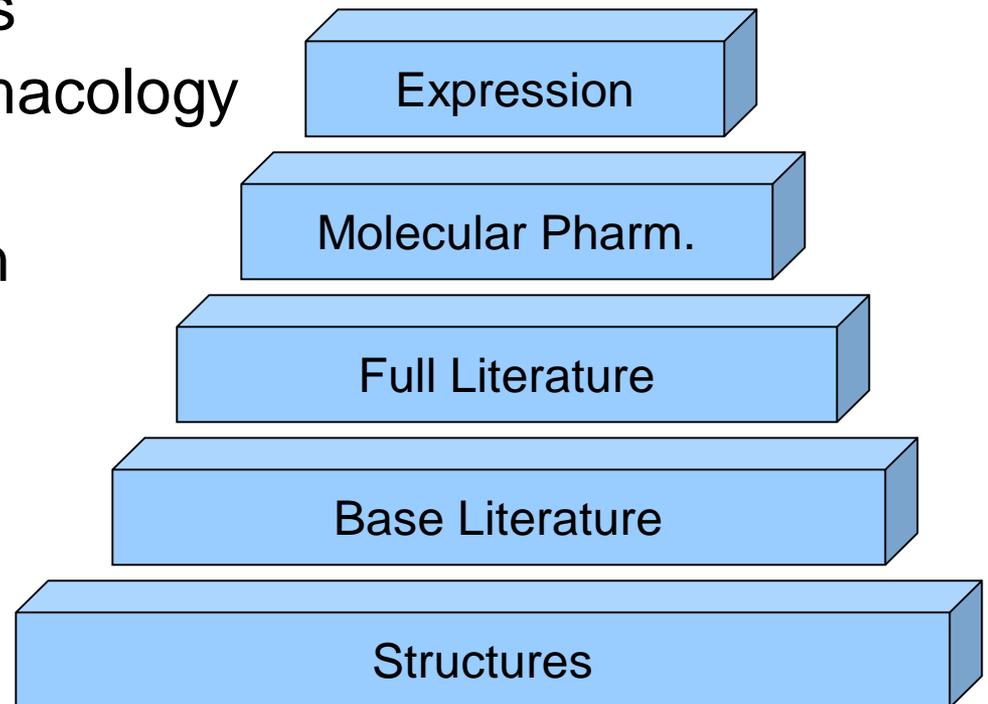




Progression of Content

Numbers of Compounds:

- 637 in Expression Studies
- 867 with Molecular Pharmacology
- ~900 with Full Curation
- ~2000 with Base Curation
- ~8000 with Structures

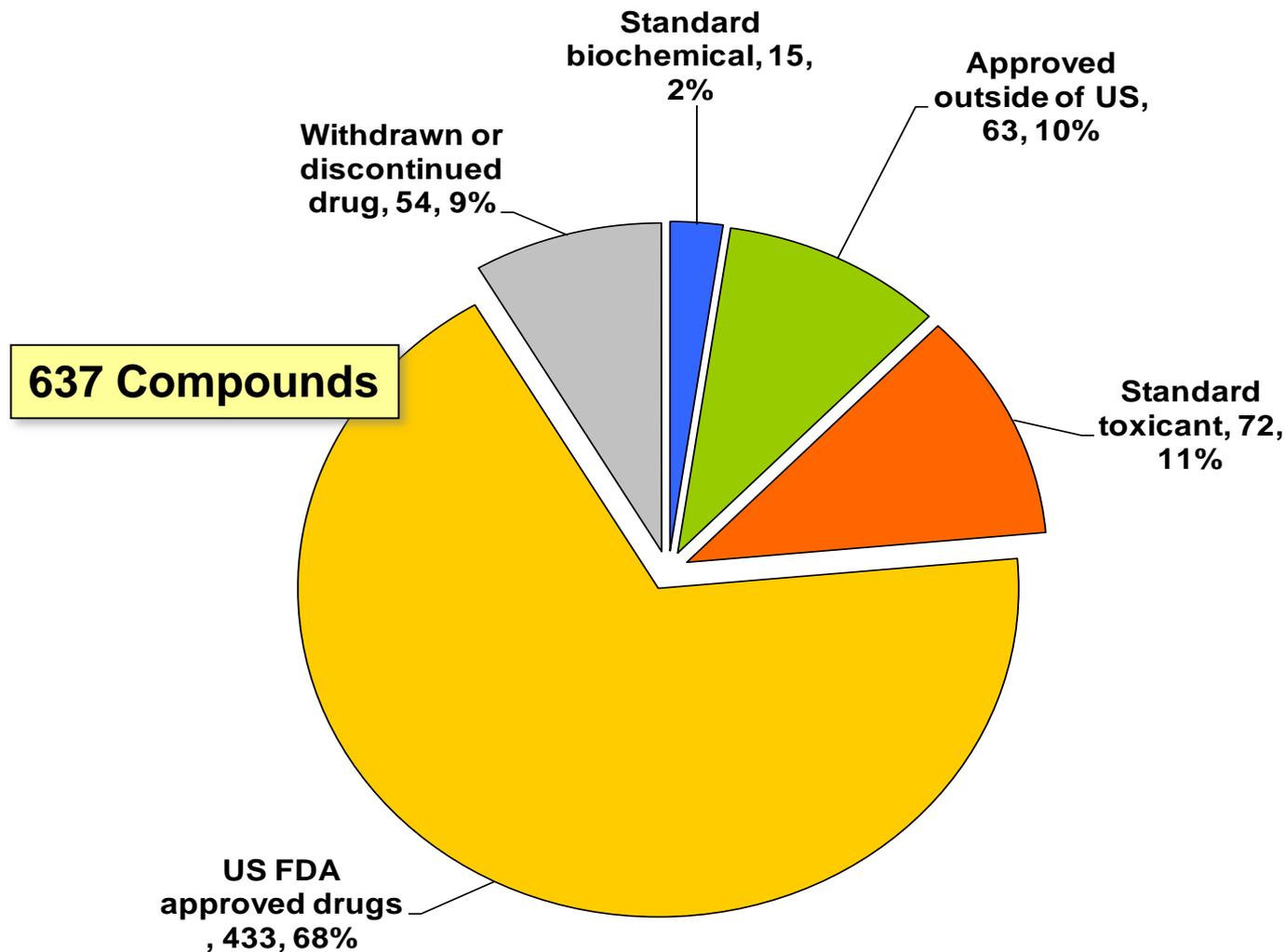




DrugMatrix Gene Expression Data

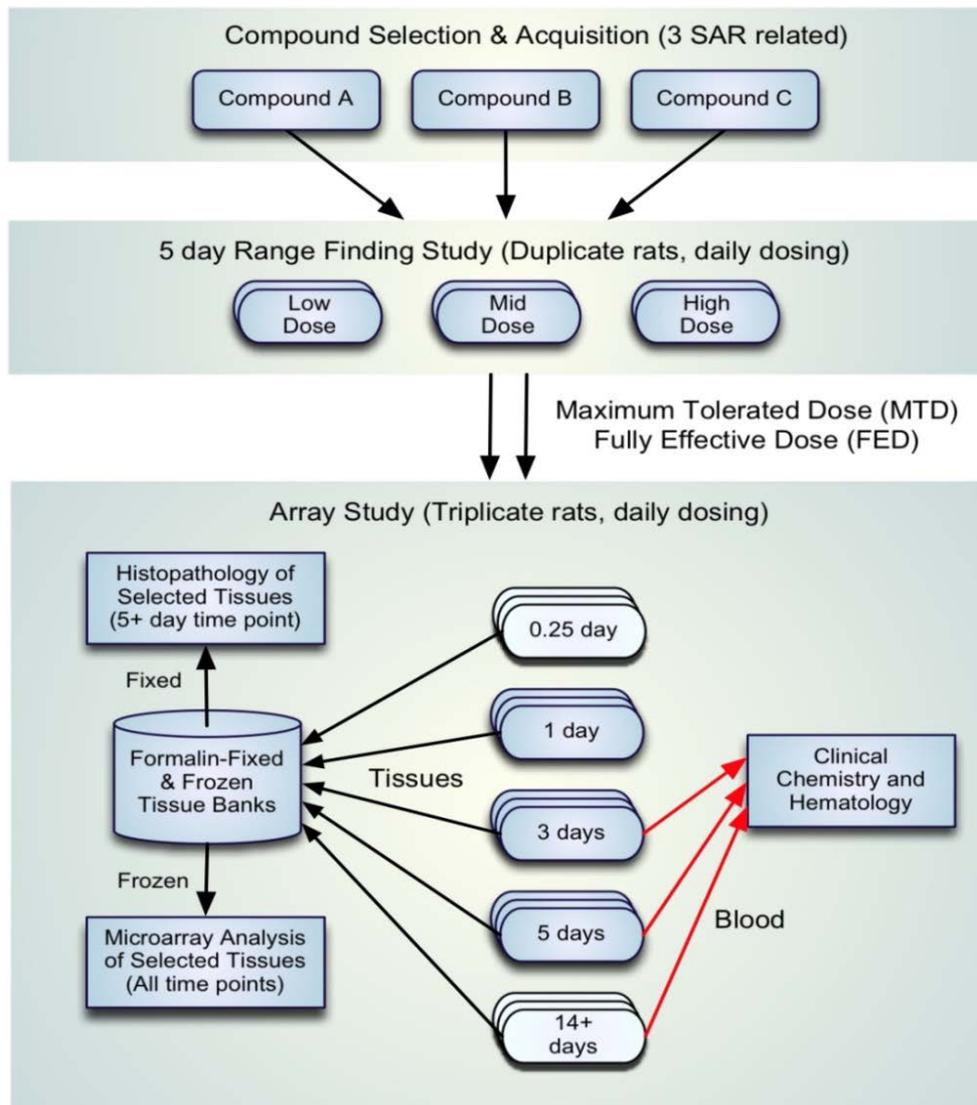


DrugMatrix Chemical Diversity



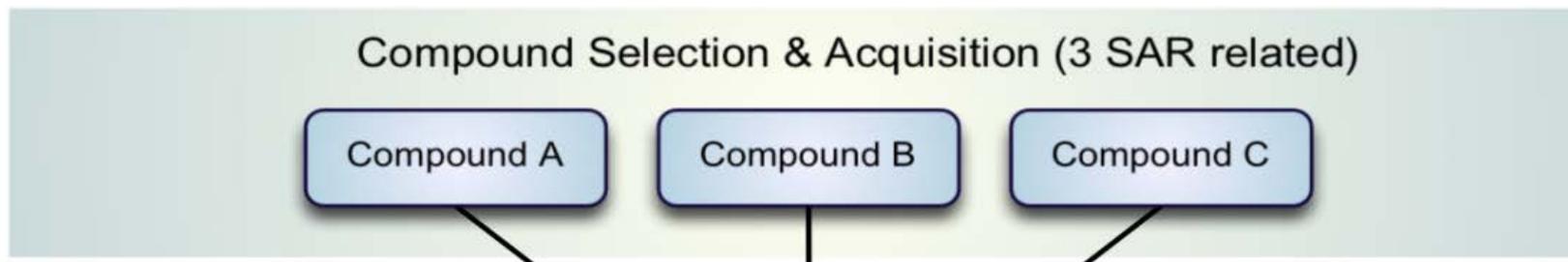


Standardized DrugMatrix *in vivo* Experimental Protocol





Chemical Selection



- Goal is to identify biomarkers predictive of pathology
- Cannot have drug mechanism confounded with tox mechanism
- Minimal designs require 3 mechanistically/structurally distinct classes



Range Finding Study

5 day Range Finding Study (Duplicate rats, daily dosing)

Low
Dose

Mid
Dose

High
Dose

- Dosing was estimated from literature curation
- Literature information was used to estimate an MTD dose
 - MTD: 10% reduction in growth (body weight)
- Dose estimate was bracketed for a 5 day range finding study
- Results of range finding study often differed from the literature
- Results were presented to the dose-setting committee
- Committee approves dosing for array study

Dose Justification: Example

DOSE JUSTIFICATION

Note: The final low array dose choice was based on a rat model for gastric ulcer formation and motor co-ordination.

High Array Dose Recommendation
At the high RF dose (54mg/kg/day), weight gain was 21.3%. No clinical signs were displayed by any animals at any of the doses. Animals gained 21.4% body weight at the mid (32mg/kg/day) and 19.2% body weight at the low (16mg/kg/day) RF doses. It has been decided to use the high RF dose as the high array dose.

Low Array Dose Recommendation
Phenobarbital is indicated for gastrointestinal disturbances such as cramps, spasms, diarrhea, nausea, vomiting and peptic ulcer. It is also indicated as a treatment for irritable bowel syndrome and is a potent anesthetic/anti-convulsant. Human dose is 125mg/day (PDR). This scales to 7mg/kg/day in the rat. 50mg/kg/day for 10 days was administered to rats with chronic gastric ulcer. This dose significantly increases cytochrome P-450 in the gastric mucosa, which results in the stimulation of mucosal barrier protective glycoproteins (PMID 9206565 - abstract only).

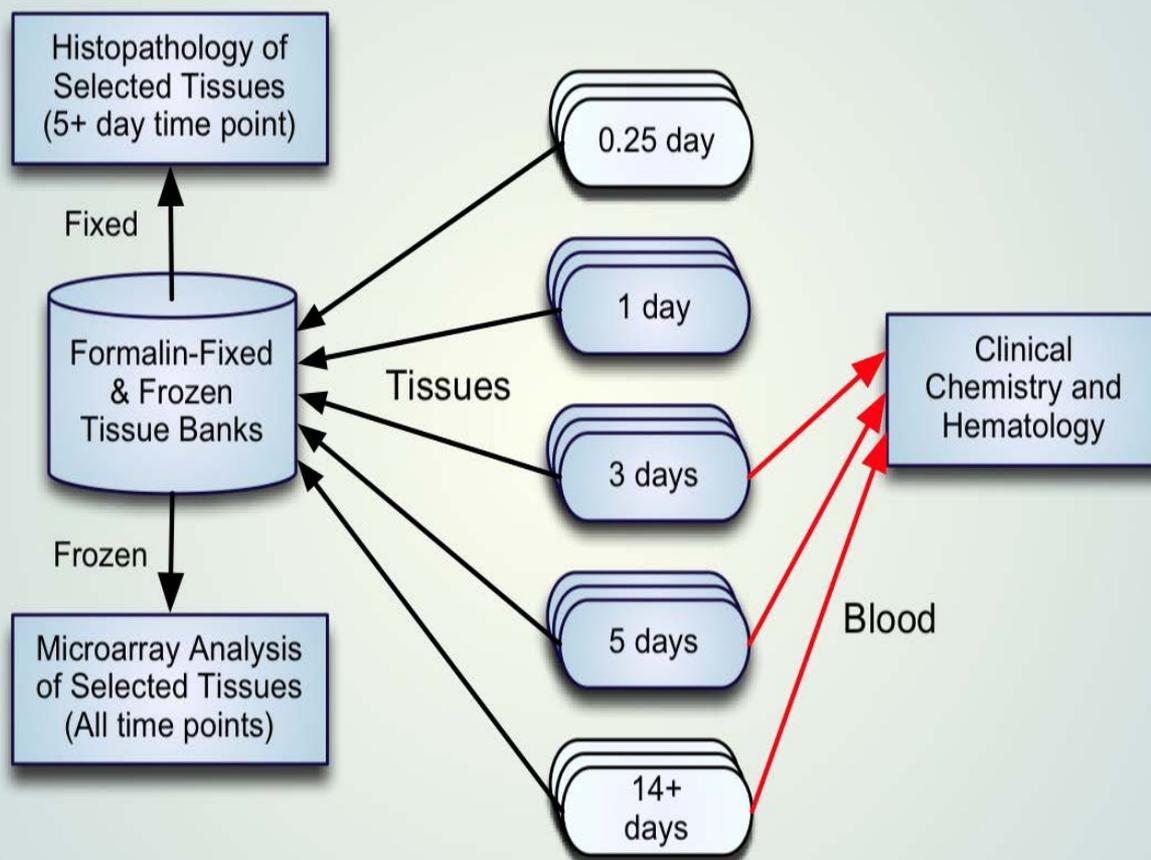
Gastric ulcers were induced in rat glandular stomach by the cold-restraint method. The fore and hind limbs are tied together with metallic wire and the rats are left in a 4°C incubator for 2 hours. An oral dose of 50mg/kg gave 78% protection against ulcer formation under these conditions. 20mg/kg resulted in 33% protection and 10mg/kg resulted in 11% protection. Rats are also trained to walk on a rotating rod. The reduction in locomotor activity caused by Phenobarbital administration is reflected in the % of animals that fall off the rod in 2 minutes. 100mg/kg Phenobarbital will cause 100% of the rats to fall off the rod; 50mg/kg cause 70% to fall; 25mg/kg causes 40% to fall (PMID 2860988). 25mg/kg/day administered in the rat diet for 2 weeks resulted in significant induction of hepatic cytochrome P450 (PMID 1554380 - article retrieved).

I recommend that we use 25mg/kg/day as the low array dose, which would protect against gastric ulcer formation (50mg/kg/day) is too close to the high array dose. Floater tissue should be the brain.

All recommendations were accepted at the dose-setting meeting 12-17-01.

Definitive DrugMatrix Array Study

Array Study (Triplicate rats, daily dosing)

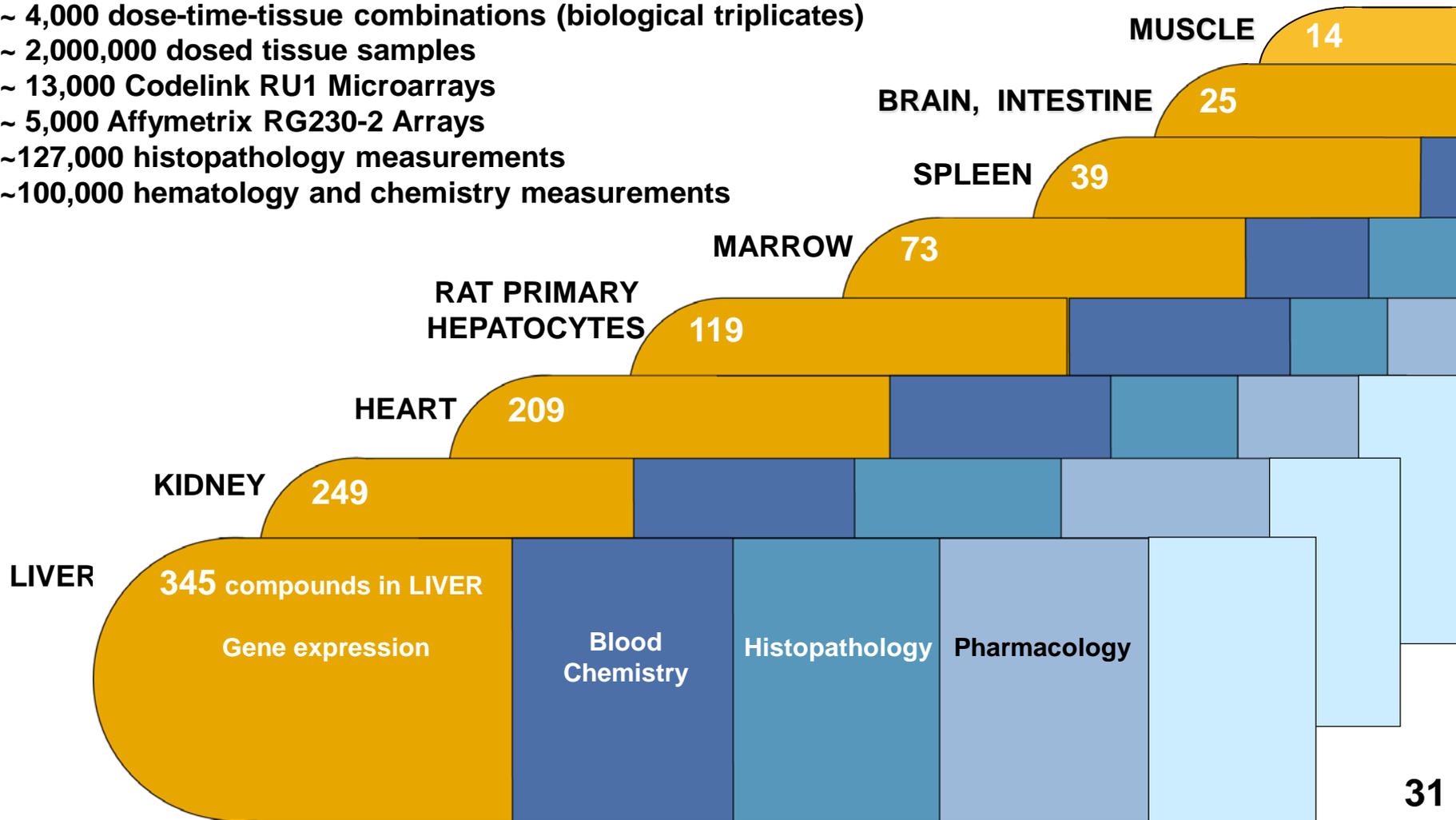


- Two doses
 - MTD
 - FED
- Four time points
 - 0.25
 - 1
 - 3
 - 5, 7, or 14
- Daily dosing every morning at ~ same time
- Sacrifice in morning at ~ same time (except 0.25d)
- Tissues collected
 - Punches flash frozen
 - Part fixed in formalin



DrugMatrix Content

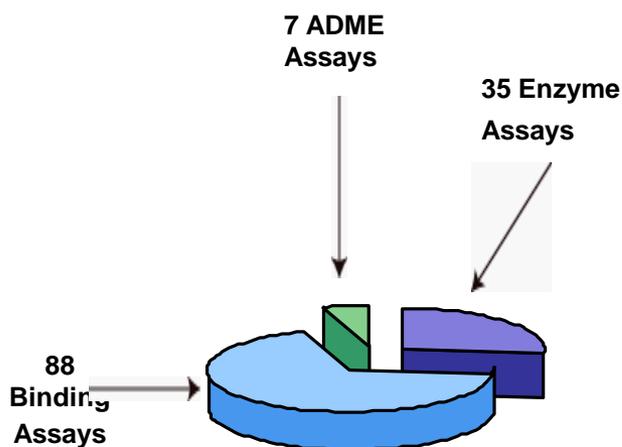
- ~ 637 compounds
- ~ 4,000 dose-time-tissue combinations (biological triplicates)
- ~ 2,000,000 dosed tissue samples
- ~ 13,000 Codelink RU1 Microarrays
- ~ 5,000 Affymetrix RG230-2 Arrays
- ~127,000 histopathology measurements
- ~100,000 hematology and chemistry measurements





Molecular Pharmacology Profiles

- Over 870 compounds profiled across 130 *in vitro* pharmacology assays



DOXORUBICIN

> SMILES > SYNONYMS > IDENTIFIERS > PHYSICAL PROPS.

SIMILAR INDUCED REPRESSED EXPERIMENTS **ACTIVITIES** LITER. TARGET MOTIF

> I MENU **BIO-ACTIVITIES**

| ASSAY | | INHIBITION | IC50 | KI |
|--|-------------------------------------|------------|----------|----------|
| Protein Tyrosine Kinase, HER2 Receptor | <input checked="" type="checkbox"/> | 100.0% | 2.485uM | |
| Protein Tyrosine Kinase, Fyn | <input checked="" type="checkbox"/> | 98.0% | 5.147uM | |
| Serotonin 5-HT4 | <input checked="" type="checkbox"/> | 82.0% | 12.468uM | 2.078uM |
| Sodium Channel, Site 2 | <input checked="" type="checkbox"/> | 75.0% | 15.245uM | 13.668uM |
| Protease, Caspase 1 | <input checked="" type="checkbox"/> | 73.0% | 12.192uM | |
| Lipoxygenase 15-LO | <input checked="" type="checkbox"/> | 73.0% | 13.59uM | |
| Protein Tyrosine Kinase, Lck | <input checked="" type="checkbox"/> | 61.0% | 31.913uM | |
| Muscarinic M1 | <input checked="" type="checkbox"/> | 53.0% | 15.336uM | 3.693uM |
| Serotonin 5-HT1B | <input checked="" type="checkbox"/> | 52.0% | 34.464uM | 15.666uM |



DrugMatrix - In vitro Assays

- 125 biochemical assays of receptors, ion channels and enzymes
- Assays were selected to include assays of drug targets with known side effects potentially undesirable for new drug candidates, assays of targets for very important drug classes, assays for targets popular within the drug industry and sites of human drug-drug interaction and human drug metabolism
- Sixty-nine percent (69%) of the assays are based on expression of the human recombinant form of the receptor or enzyme
- Rat-based assays comprise 14% of the assays, and the remainder comprises mouse, bovine, bacteria, guinea pig, and rabbit-based assays
- Assay Protocol
 - Tier 1: ~861 screened at 10 μ M
 - Tier 2
 - Compounds were selected for more extensive testing if they achieved or exceeded 70% inhibition at the 10 μ M concentration
 - eight concentrations at $\frac{1}{2}$ -log intervals in duplicate

Literature and Structure Curation

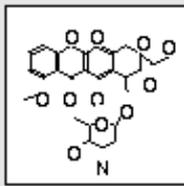
- Clinical literature
 - indication, mechanism, toxicity
- Pharmacology literature
 - ED50, LD50, IC50
- Pharmacokinetic literature
 - CMax, half-life, AUC, Clearance
- Physical properties
 - MW, logP, logS, pKa
- Structure files
 - .mol files

DETAIL CURATION PHARMA. PATH

DETAIL

Compound: DOXORUBICIN

Molecular Structure:



Molecular Weight: 544

Formula: C₂₇ H₂₉ N O₁₁

Development Status: US FD Approved

DETAIL CURATION PHARMA. PATH

COMPOUND CURATION

Mechanism:
Inhibit DNA synthesis, repair, and function

Mode Class:
Distorts /blocks macromolecular synthesis scaffold

Known Toxicity:
Carcinogenicity
Mutagenicity
Blood & Bone Marrow Toxicity
Cardiovascular Toxicity

Tissue Toxicity:
Carcinogenicity
Mutagenicity
Hemorrhage
Cardiomyopathy
Cardiotoxicity
Congestive Heart Failure
Myelosuppression

Adverse Effect:
REP_3_Testicular Atrophy
IMU_2_Urticaria
XXX_1_Infection
CVS_1_Cardiotoxicity
CVS_1_Cardiomyopathy
SKN_1_Alopecia / Hair Loss
BBM_3_Acute Leukemia

| COMPOUND PHARMACOLOGY | |
|-----------------------|-----------------------|
| DETAIL | CURATION PHARMA. PATH |
| ANTOX, LD50 | 10.5 mg... |
| ANTOX, LD50 | 16 mg/kg |
| ANTOX, Observed T... | 10 mg/kg |
| ANTOX, Observed T... | 25 mg/kg |
| ANTOX, TDLo (Time... | 12 mg/kg |
| ANTOX, TDLo (Time... | 15 mg/kg |
| ANTOX, TDLo (Time... | 21 mg/kg |
| ANTOX, TDLo (Time... | 24 mg/kg |
| CLNPH, AUC | .413 mg... |
| CLNPH, Clearance | 71.4 L/h |
| CLNPH, Cmax | .0426 m... |
| CLNPH, Cmax | 4.5 mg/L |
| CLNPH, Effective ... | 75 mg/m... |
| CLNPH, Half_Life | 30 h |
| CLNPH, Half_Life | 47 h |
| VVPH, Eff Conc | 4 mg/kg |



Recent Updates to Drug Matrix

- Normalization: MAS5 to PLIER
- Signatures were rederived after normalization update
- Ongoing: Gene annotation updates
- Ongoing: GO term updates
- Ongoing: Add TG-GATES data



DrugMatrix Data Domains

- [Gene Domain](#) – search individual genes to find out how they behave with different treatments
- [Assay Domain](#) – search and display in vitro assay results and clinical chemistry/hematology results
- [Expression Domain](#) – view results for single expression studies
- [Pathway Domain](#) – explore over 130 different biological pathways
- [Expression Study Domain](#) – view composite results multi-day/dose toxicity/toxicogenomic studies
- [Signature Domain](#) – Search predefined genomic signatures in DrugMatrix
- [Histopathology Domain](#) – Find details on specific histopathologies annotated in DrugMatrix
- Motif Domain – Search DrugMatrix Motif Signatures that are based solely on genes annotated to biological pathways



DrugMatrix ToolBox

- [Significant Gene Finder](#) - find differentially expressed genes
- [Expression Experiment Matrix](#) - cluster your data with other DrugMatrix data
- [Pathway Impact Matrix](#) - cluster pathway impact scores
- [Hypergeometric Analysis](#) - identify enriched DrugMatrix ontologies for compounds that exhibit similar gene expression patterns
- [Pattern Creator](#) - generate your own gene expression biomarkers
- [Pattern Assessment](#) - estimate the performance of your gene expression biomarker
- [Signature Heatmap](#) and [Signature Histogram](#) - score your data with predefined DrugMatrix signatures



DrugMatrix/ToxFX Related Publications (1)

- Ganter, B., Tugendreich, S., Pearson, C. I., Ayanoglu, E., Baumhueter, S., Bostian, K. A., Brady, L., Browne, L. J., Calvin, J. T., Day, G. J., Breckenridge, N., Dunlea, S., Eynon, B. P., Furness, L. M., Ferng, J., Fielden, M. R., Fujimoto, S. Y., Gong, L., Hu, C., Idury, R., Judo, M. S., Kolaja, K. L., Lee, M. D., McSorley, C., Minor, J. M., Nair, R. V., Natsoulis, G., Nguyen, P., Nicholson, S. M., Pham, H., Roter, A. H., Sun, D., Tan, S., Thode, S., Tolley, A. M., Vladimirova, A., Yang, J., Zhou, Z. and Jarnagin, K. (2005). Development of a large-scale chemogenomics database to improve drug candidate selection and to understand mechanisms of chemical toxicity and action. *J Biotechnol* 119, 219-44.
- Roter, A. H. (2005). Large-scale integrated databases supporting drug discovery. *Curr Opin Drug Discov Devel* 8, 309-15.
- Fielden, M. R., Eynon, B. P., Natsoulis, G., Jarnagin, K., Banas, D. and Kolaja, K. L. (2005). A gene expression signature that predicts the future onset of drug-induced renal tubular toxicity. *Toxicol Pathol* 33, 675-83.



DrugMatrix/ToxFX Related Publications (2)

- Natsoulis, G., El Ghaoui, L., Lanckriet, G. R., Tolley, A. M., Leroy, F., Dunlea, S., Eynon, B. P., Pearson, C. I., Tugendreich, S. and Jarnagin, K. (2005). Classification of a large microarray data set: algorithm comparison and analysis of drug signatures. *Genome Res* **15**, 724-36.
- Tugendreich, S., Pearson, C. I., Sagartz, J., Jarnagin, K. and Kolaja, K. (2006). NSAID-induced acute phase response is due to increased intestinal permeability and characterized by early and consistent alterations in hepatic gene expression. *Toxicol Pathol* **34**, 168-79.
- Fielden, M. R., Brennan, R. and Gollub, J. (2007). A gene expression biomarker provides early prediction and mechanistic assessment of hepatic tumor induction by nongenotoxic chemicals. *Toxicol Sci* **99**, 90-100
- Fielden, M. R. and Halbert, D. N. (2007). Iconix Biosciences, Inc. *Pharmacogenomics* **8**, 401-5.
- Natsoulis, G., Pearson, C. I., Gollub, J., B, P. E., Ferng, J., Nair, R., Idury, R., Lee, M. D., Fielden, M. R., Brennan, R. J., Roter, A. H. and Jarnagin, K. (2008). The liver pharmacological and xenobiotic gene response repertoire. *Mol Syst Biol* **4**, 175.

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- SRA

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- Dan Whitley
- Tony Calore
- Henry Norris

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| Alexander M. Tolley | Richard Tso | Stuart Tugendreich | Antoaneta Vladimirova | Bonnie Wong |
| Jian Yang | Zhiming Zhou | | | |